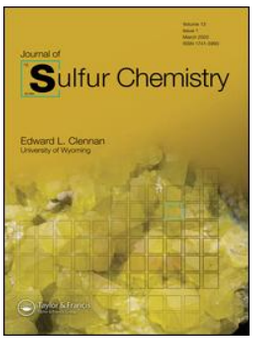

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BRIEF REPORT

Cleaner and greener synthesis of 3*H*-benzothiazole-2-thione and its derivatives

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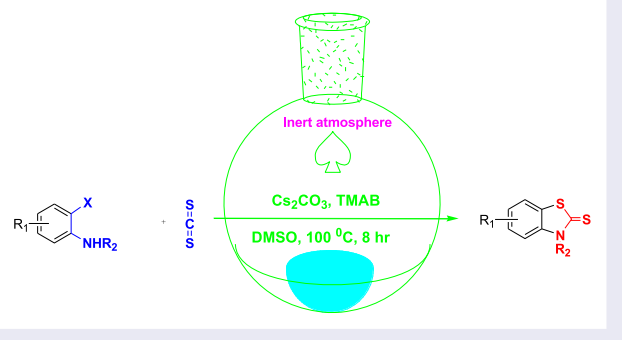
ABSTRACT

A cleaner and greener method of synthesis of 3*H*-benzothiazole-2-thione is being reported in this communication. In this method, various *o*-iodoaniline derivatives are reacted with carbon disulfide in the presence of Cs_2CO_3 and tetramethyl ammonium bromide (TMAB) to give 3*H*-benzothiazole-2-thione and its derivatives in higher yields.



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KEYWORDS
3*H*-benzothiazole-2-thione; carbon disulfide; tetramethyl ammonium bromide; *o*-iodoaniline

1. Introduction

3*H*-benzothiazole-2-thiones are significant synthons forming the basic structures used in pharmaceuticals. They have shown potential fungicidal [1], anti-yeast [2,3], anti-candida [4,5], anti-bacterial [6], anti-inflammatory [7], anti-hypertension [8], anti-tumor [9] activities, etc. Earlier investigations have revealed that 2nd, 5th, and 6th substitutions in benzothiazole and 2-mercaptobenzothiazole have shown significant fungicidal and microbicidal properties. It has also been revealed that if 6th position is substituted with electron withdrawing groups like halogens, trifluoromethyl, nitro, amino, fungicidal, and microbicidal activities are enhanced [10]. Azam and Suresh [11] in their literature review have mentioned that the pharmacological activity of these systems has been widely investigated and is found to be efficient. In a very early study, Halasa and Smith suggested

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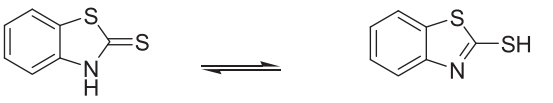
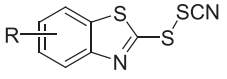
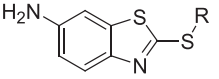


3*K*-Benzothiazole-2-thione Benzothiazole-2-thiol

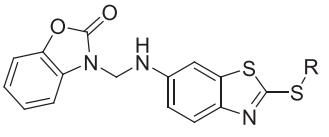
Figure 1. Tautomeric forms of the benzothiazole-2-thiol ring system.



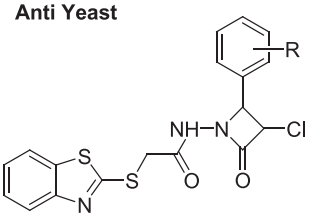
R= CH_3, OH, NO2, Br, Cl, H
Fungicide



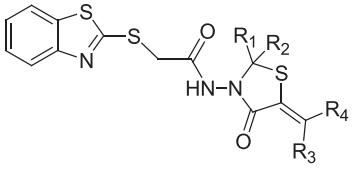
R= $-CH_2CH=CHCH_3$, $(CH_2)_3CH=CH_2$
Anti Yeast



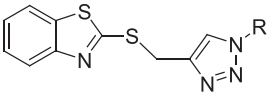
R= Allyl, C_2H_5, CH_3,
Anti Candida



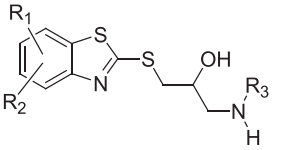
R= 4-OH, 4-Cl, 3-OH, 4-NO_2, 2-OH, 4-OCH_3
Bactericidal



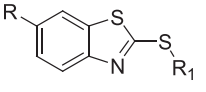
R_3= R_1= H, CH_3
R_2 = R_4= 4-NO_2, 2-OH, 4-Cl, 4-OCH_3
Anti inflammatory



R= C_6H_5, 4-F-C_6H_4, 3-Cl-C_6H_4, 2-Cl C_6H_4, 4-NO_2 C_6H_4,
Antipyretic comparable to Ibuprofen



R_1= H, Cl, NO_2, COOH, $NHCOCH_3$
R_2= H,CH_3, NH_2, NO_2
R_3= $CH(CH_3)_3$, $CH_2CH_2(CH_3)_2$, $CH(CH_3)_3$
Antihypertensive



R = H, F, NO_2, CF_3, OCH_3, OCH_2CH_3
R_1= H, CH_2-CH_3
Anti tumor

Figure 2. Some bioactive benzothiazole derivatives.

that the benzothiazole-2-thiol ring system is in a tautomeric form with benzothiazole-2-thione (Figure 1) and Michael/Mannich reactions could easily be performed to produce *N*-substituted benzothiazole-2-thione compounds [12,13] (Figure 2).

The traditional methods for the synthesis of 3*H*-benzothiazole-2-thione made the use of the reactions between *N*,*N*-diphenylthioureas and sulfur. In the other ways, its synthesis was done by the reaction of carbon disulfide with 2-aminobenzenethiols under extreme

pressure [14]. Later these classes of compounds were synthesized by nucleophilic aromatic substitution (S_NAr) reaction *O*-ethyldithiocarbonate anion with an *o*-haloaniline and subsequently ring closure [15]. These methods involve extreme conditions [16], toxic chemicals, tiring workup, and lesser yields [17]. So owing to the significance of 3*H*-benzothiazole-2-thione in various fields, a better, cleaner, and greener method with high yield is always welcomed. Here, an effort to prepare different 3*H*-benzothiazole-2-thione is being reported. This method is cleaner and greener compared to the existing methods.

2. Results and discussion

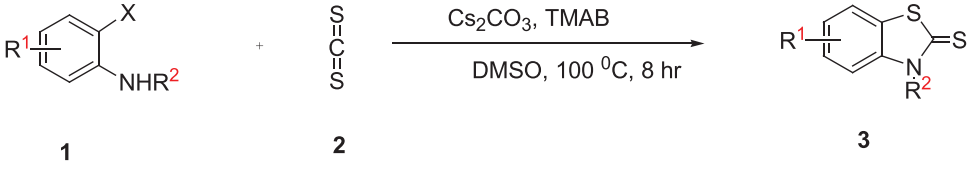
All the chemicals used in this process are either easily available in the market or may be easily synthesized in the laboratory. In this method, an easily available carbon disulfide, 2-iodo- or 2-bromoanilines are employed as starting materials and gives the corresponding 3*H*-Benzothiazole-2-thione in higher yields in mild conditions in easier and simpler method. The reaction with 2-iodoaniline derivatives proceeded easily as compared to 2-bromoaniline derivatives. So in order to make the process energy efficient and enhance general suitability, 2-iodoaniline derivatives were used for the synthesis. During the performance of the process, it was found that 2-chloroaniline derivatives did not reacted with the CS_2 in the presence of Cs_2CO_3 and tetramethyl ammonium bromide (TMAB) even on increasing the temperature to 200°C. On the basis of such screening, we found that the 2-iodoaniline derivatives are more suitable for a cleaner and greener process and so we proceeded with 2-iodoanilines. Here the reaction was carried under the inert atmosphere. The phase transfer catalyst enhances the mutual interaction among the reactants and is easily removed from the product. Cs_2CO_3 was chosen because it is cheap, mild base, easily available, highly soluble in both polar and non-polar solvents and easily separated from the reaction mixture.

According to the planned reaction, we took 2-$IC_6H_4NH_2$ in a 50 mL sealing tube and added tetramethyl ammonium bromide (TMAB), CS_2 and Cs_2CO_3 to it. Now 10 mL of DMSO was added under inert atmosphere and was thoroughly mixed for 30 min. Further, this was stirred at higher temperature of 100°C for 08 h after sealing. Now the tube was cooled to room temperature and further added with some water. Then the organic compound was extracted, concentrated, and purified. Compounds formed (entry 3a, Table 2) were identified by spectral and physical data. IR spectrum of **3a** showed absorption band representing unsaturation at 1602 cm^{-1}, C = S at 1340 and 1185 cm^{-1}. Proton spectra of entry **3a** showed broad peak at $\delta = 13.76$ (N–H), aromatic protons multiplet in the range $\delta = 6.30$–6.93. The ^{13}C spectra also confirmed the presence of C = S, C–S, C–N bonds in the synthesized compounds. The mass and elemental constitution of the product confirmed by HRMS (*m/e*) = 167.9938(obs.), 167.9931(calc). Thus the compound formed was confirmed as 3H-Benzothiazole-2-thione.

The outcome of this product (entry 3a, Table 2) was evaluated with various phase transfer catalyst by reacting *o*-iodoaniline with carbon disulfides in different phase transfer catalyst. We tried many phase transfer catalyst like tetra-*n*-butyl ammonium chloride (TBAC), tetramethyl ammonium bromide (TMAB), tetra-*n*-butyl ammonium bromide (TBAB), tetra-*n*-butyl ammonium iodide (TBAI), tetra-*n*-butyl ammonium hydrogen carbonate (TBAHC), tetra-*n*-butyl ammonium hydrogen sulfate (TBAHS), Triton-B, crown

Table 1. Effect of different catalyst on time and yield of the product.

S. no.	Phase transfer catalyst	Time (h)	% Yield
1	TBAC	10.0	72
2	TMAB	8.0	80
3	TBAB	9.0	75
4	TBAHC	12.0	72
5	TBAHS	14.0	70
6	Triton-B	9.0	75
7	Crown ether (18 Crown 6)	11.0	72



1 2 3

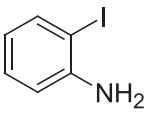
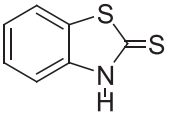
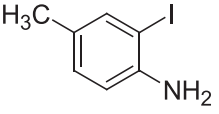
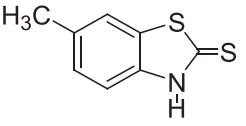
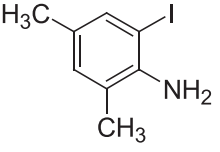
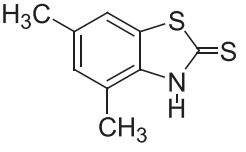
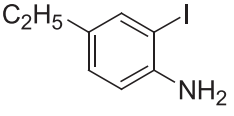
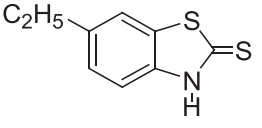
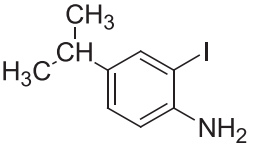
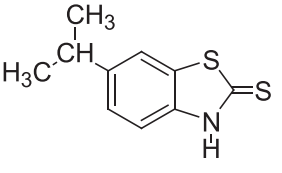
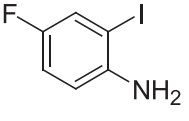
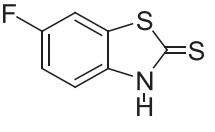
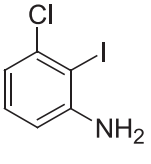
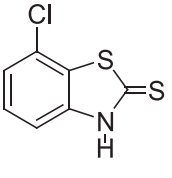
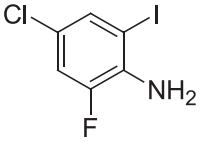
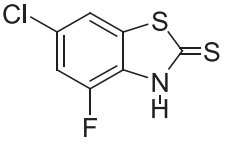
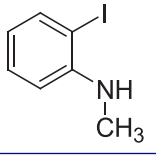
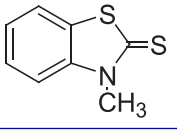
X= I
R^1= -CH_3, -C_2H_5, -F, -Cl etc
R^2= -CH_3, -C_2H_5, *iso*-C_3H_7, -Ph, etc

Scheme 1. Synthesis of 3H-benzothiazole-2-thiones.

ether (18 crown 6), etc. It was found that tetramethyl ammonium bromide (TMAB) served well in getting high yield of the desired 3*H*-benzothiazole-2-thione (Table 1).

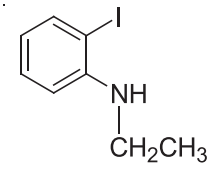
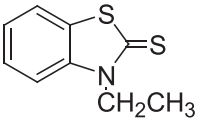
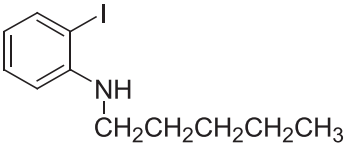
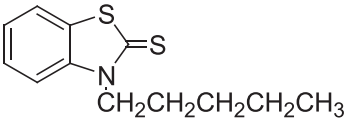
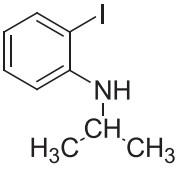
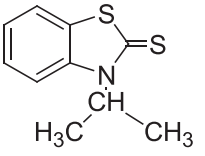
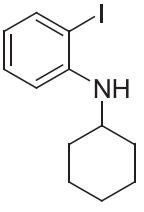
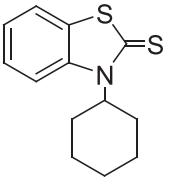
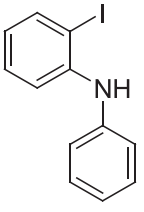
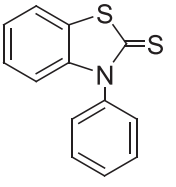
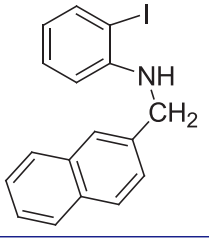
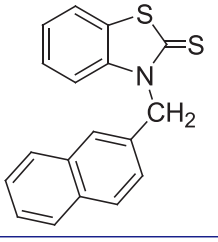
After optimizing the reaction conditions *o*-iodoanilines with different substituent on the aromatic ring and *N*-substituted *o*-iodoanilene with different groups like alkyl (primary, secondary, tertiary), alicyclic, aromatics were employed in tetra methyl ammonium bromide and CS_2 system in DMSO to get various benzothizole-2-thiones. It was also observed that electron releasing group on the aromatics ring gave better yield and in lesser time as compared to the electron withdrawing groups attached to aromatic ring. Here in this reaction several products were formed which involved weak electron-attracting groups (e.g. –Br) to strong electron-attracting groups (e.g Fluoro), along with electron-repelling substituents like CH_3 in the *para*-position. The substituents in *para* and *ortho* position with respect to NH_2 group gave higher yields of the corresponding product (entries **3d** and **3e**). To study the effect of various *N*-substituted anilines on the product, we tried various *o*-iodoanilines in which one of the H of amino group substituted with 1°, 2°, 3° alkyl group, phenyl, benzylic and cyclic groups and reacted them with CS_2 in the presence of TMAB and CS_2CO_3. It was found that with *N*-substituted iodoanilines the yield was also very good. *N*-methyl iodoaniline gave 3-methyl-3*H*-benzothiazole-2-thione **3i**, the yield was 94% at 100°C (Scheme 1). Same method yielded 84% of 3-ethyl-3*H*-benzothiazole-2-thione **3j**. It can be stated here that electron releasing group at *N* gave higher yield in lesser time. Simultaneously crowding at N decreases the yield and increases the time of the reaction. The spectral characterization of all benzothiazoles and their substituted analogues were confirmed through the standard data available for the existing compounds in the literature [18–21]. Various synthesized compounds are summarized in Table 2.

Table 2. Synthesized 3*H*-benzothiazole-2-thione and its derivatives.

Entry	*o*-iodoaniline	Product	Time (h)	% Yield
3a			8.0	80
3b			8.0	78
3c			9.2	92
3d			11.5	91
3e			11.0	93
3f			14.0	86
3g			13.0	88
3h			15.0	84
3i			8.0	94

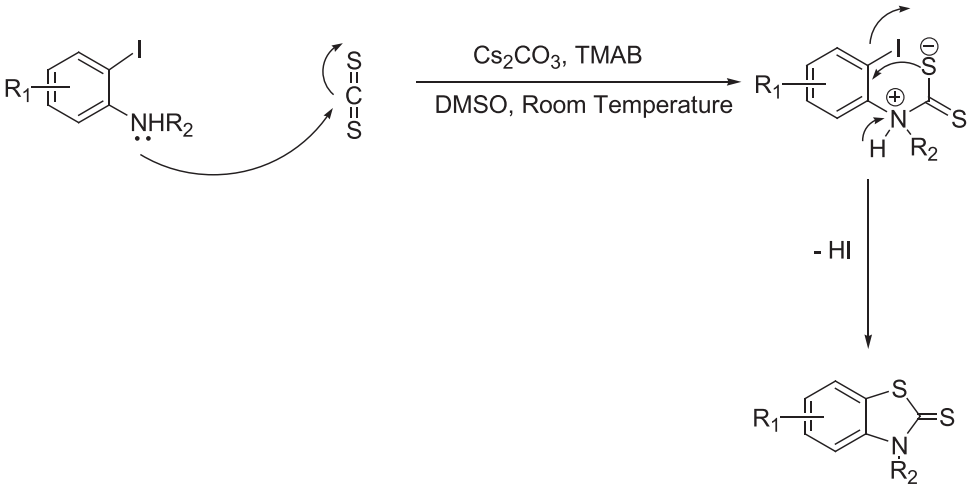
(*continued*).

Table 2. Continued.

Entry	*o*-iodoaniline	Product	Time (h)	% Yield
3j			9.0	84
3k			11.5	80
3l			11.0	80
3m			20.0	70
3n			10.0	80
3o			28.0	85

3. Possible mechanism

The probable mechanism of the reaction of iodo anilines with carbon disulfide is given in Scheme 2.



Scheme 2. Possible mechanism of the reaction.

Here the lone pair of e^- on N atom of aniline attacks the electrophilic site generated on the CS_2 due to the displacement of the electron to more electronegative Sulfur atom and subsequent intramolecular S_NAr reaction forms Benzothiazole-2-thione [22].

4. Experimental

All chemicals used in the reaction were procured from Fluka, Merck, and Sigma Aldrich. No further purification of the procured reagents was done. Silica gel (10–40 mm particle size) was used for column chromatography. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker advance DPX instrument at 400, 100 MHz respectively at room temperature in $CDCl_3$. X-4 digital melting point apparatus with microscope was used to ascertain the melting points of the compounds. Bruker Esquire ion-trap mass spectrometer was used to register mass spectra.

4.1. Typical procedure for 3H-benzothiazole-2-thione

1.095 g (5 mmol) of 2-$IC_6H_4NH_2$ was taken in a 50 mL sealed tube and added with 1.5 mL (10.0 mmol) tetramethyl ammonium bromide (TMAB), 1.0 mL (15 mmol) CS_2, and 10 mmol of Cs_2CO_3. 10 mL of DMSO was added under inert atmosphere and was thoroughly mixed for 30 min. Further, this was stirred at higher temperature of 100°C for 8 h after sealing. Now the tube was cooled room temperature and further added with 20 mL H_2O. Then the organic compound was extracted with 3 × 20 mL of ethyl ethanoate and the extracts thus obtained were dried with Na_2SO_4 (anhyd.) which was further concentrated over rotatory evaporator and chiller plant. Now the organic compound was finally obtained in pure form by silica gel packed column chromatography in which the column was eluated with hexane–ethyl ethanoate in the ratio of 5:1. The filtrate on concentration gave benzothiazole-2-thione.

4.2. Data analysis for synthesized 3H-benzothiazole-2-thione and its derivatives

1. 3*H*-Benzothiazole-2-thione [18] **(3a)**
White compound; Yield (0.667 g, 80%), melts at 188–189°C; ^{1}H NMR, δ = 13.76 (br s, 1 H), 6.30–6.93 (4H aromatic); ^{13}C NMR, δ = 189.8, 141.3, 129.4, 127.2, 124.3, 121.8, 112.5; HRMS (*m/z*) for [$C_7H_5NS_2 + H^+$] = 167.9938 (Obs.), 167.9931.

2. 6-Methyl-3*H*-benzothiazole-2-thione [18] **(3b)**
White compound; Yield (0.70 g, 78%), melts at 179–180°C; ^{1}H NMR, δ = 13.68 (s, br, NH), 7.44 (s, 1 H), 7.20 (s, 2H), 2.29 (s, CH_3); ^{13}C NMR δ = 189.2, 138.8, 134.0, 129.5, 127.9, 121.6, 112.2, 20.8; HRMS (*m/z*) for [$C_8H_7NS_2 + H^+$] = 182.0088 (obs.), 182.0093 (calc.).

3. 4,6-Dimethyl-3*H*-benzothiazole-2-thione [19] **(3c)**
White compound; Yield (0.89 g, 92%), melts at 184–185°C; ^{1}H NMR, δ = 13.64 (br, 1H, NH), 6.54 (1H singlet aromatic), 6.40 (1H singlet aromatic), 2.35 (6H singlet,); ^{13}C NMR δ = 196.1, 137.8, 134.7, 133.7, 129.1, 127.2, 127.0, 21.1, 11.7; HRMS (*m/z*) for [$C_9H_9NS_2 + H^+$] = 195.0245 (obs.), 196.0248 (calc.).

4. 6-Ethyl-3*H*-benzothiazole-2-thione [15**(d)**] **(3d)**
Yellow oil; Yield (0.78 g, 80%); ^{1}H NMR, δ = 7.48, 7.29, 7.21, 4.41, 1.78-1.84 (m, 2H), 1.42–1.48 (2H, m), 1.35–1.38 (2H, m), 1.27–1.34 (m, 6H), 0.88; ^{13}C NMR, δ = 188.9, 141.5, 127.9, 126.8, 124.5, 121.3, 112.3, 46.4, 29.2, 29.1, 26.8, 26.7, 22.5, 13.9; HRMS (*m/z*) for [$C_9H_9NS_2 + H^+$] = 196.2027 (obs.), 196.2038(calc.).

5. 6-Iso propylbenzo thiazole-2(3*H*)-thione [15**(d)**] **(3e)**
Yellow oil; Yield (0.83 g, 80%); ^{1}H NMR, δ = 13.68 (s, broad N–H), 6.80–6.22 (aromatic, multiplet), 3.12 (multiplet, 2H), 1.29 (singlet 6H terminal); ^{13}C NMR, δ = 196.1, 145.0, 137.3, 129.0, 125.3, 123.4, 31.7, 24.4; HRMS (*m/z*) for [$C_{10}H_{11}NS_2$+ H^+] = 209.0333(obs.), 209.0321(calc.).

6. 6-Fluorobenzo thiazole-2(3*H*)-thione [19] **(3f)**
White compound; Yield (0.79 g, 86%), melts at 204.6–205.9°C; ^{1}H NMR, δ = 13.84 (s, N-H), 7.69 (doublet, 1H), 7.35 (double doublet, 1H), 7.28 (s, 1H); ^{13}C NMR, δ = 191.4, 142.7, 132.3, 128.7, 124.5, 123.7, 112.4; HRMS (*m/z*) for [$C_7H_4FNS_2$+ H^+] = 185.9838 (obs.), 185.9841(calc.). Consider reference no [19].

7. 7-Chlorobenzo thiazole-2(3*H*)-thione [15**(b)**] **(3g)**
White compound; Yield (0.85 g, 85%); melts at 204.6–205.9°C; ^{1}H NMR, δ = 13.79 (s, NH), 7.72 (1H, d), 7.35 (dd, 1H), 7.28 (1H, s); ^{13}C NMR, δ = 191.4, 142.7, 132.3, 128.7, 124.5, 123.7, 112.4; HRMS (*m/z*) for [$C_7H_4ClNS_2$+ H^+] = 201.9474 (obs.), 201.9468 (calc.).

8. 6-Chloro-4-Fluoro benzothiazole thione [19] **(3h)**
White compound; Yield (0.91 g, 84%); melts at 210–211°C; ^{1}H NMR, δ = 14.12 (br s, 1 H), 7.71–7.90 (m, 1 H), 7.48–7.71 (m, 1 H); ^{13}C NMR, δ = 190.8, 133.1, 128.7, 129.7, 120.7, 120.7, 117.7, 114.1; HRMS *(m/z)* for [$C_7H_3ClFNS_2$+ H^+] Mw = 219.9441(obs), 219.9452 (calc.).

9. 3-Methyl-3*H*-benzothiazole-2-thione [19] **(3i)**
White compound; Yield (1.029 g, 94%); melts at 100.3–101.9°C; ^{1}H NMR, $\delta = 7.51$ (d, 1H), 7.40–7.43 (1H, m), 7.27–7.32 (1H, m), 7.20 (d, 1H), 3.84 (s, 3H); ^{13}C NMR, $\delta = 189.2, 141.8, 127.3, 126.8, 124.8, 121.2, 112.2, 33.1$; HRMS (*m/z*) for $[C_8H_7NS_2 + H^+] = 182.0012$ (obs.), 182.0020 (calc.).

10. 3-Ethyl-3*H*-benzothiazole-2-thione [18] **(3j)**
Grey Solid (0.78 g, 80%) melts at 96–98°C; ^{1}H NMR, $\delta = 6.96–6.27$ (multiplet aromatic, 4H), 3.10 (quartet, 2H), 1.13 (triplet 3H terminal); ^{13}C NMR, $\delta = 193.4, 140.1, 129.3, 129.5, 125.6, 124.8, 46.3, 12.1$; HRMS: (*m/z*) for $[C_9H_9NS_2 + H^+] = 196.0176$ (obs.), 196.0168 (calc.).

11. 3-Pentyl-3*H*-benzothiazole-2-thione [18] **(3k)**
Yellow oil (0.83 g, 80%); ^{1}H NMR, $\delta = 6.96–6.27$ (multiplet, 4H aromatic), 3.06 (NCH_2 triplet), 1.56 (2H multiplet CH_2), 1.33 (2H multiplet CH_2), 1.29 (2H multiplet CH_2), 0.96 (t, 3H); ^{13}C NMR, $\delta = 193.4, 140.1, 129.3, 129.5, 125.6, 124.8, 53.5,29.3, 28.1, 22.8, 14.0$; HRMS: (*m/z*) for $[C_{12}H_{15}NS_2 + H^+] = 238.0722$ (obs.), 238.0720 (calc.).

12. 3-Isopropyl-3*H*-benzothiazole-2-thione [21] **(3l)**
Yellow oil (0.83 g, 80%); ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 6.96–6.27$ (multiplet, 4H aromatic), 2.97 (NCH multiplet), 1.18 (6H multiplet terminal CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 193.4, 140.1, 129.3, 129.5, 125.6, 124.8, 49.4, 20.4$; HRMS: (*m/z*) for $[C_{10}H_{11}NS_2 + H^+] = 210.0336$ (obs.), 210.0327 (calc.).

13. 3-Cyclohexyl-3*H*-benzothiazole-2-thione [18] **(3m)**
Husk color solid (0.87 g, 70%) melts at 114–116°C;$C_{13}H_{15}NS_2$; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 1.44$ (6H multiplet), 1.63 (4H multiplet), 2.64 (1H multiplet C–H), 6.19–6.99 (4H, multiplet, aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 193.4, 140.1, 129.3, 129.5, 125.6, 124.8, 53.2, 29.9, 27.1, 22.3$; HRMS (*m/z*) for $[C_{13}H_{15}NS_2 + H^+] = 250.0639$ (obs.), 250.0646 (calc.).

14. 3-Phenyl-3*H*-benzothiazole-2-thione [18] **(3n)**
Pale yellow oil (0.972 g, 80%); $C_{13}H_9NS_2$; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 6.39–7.03$ (5H multiplet aromatic), 6.28–6.88(4H multiplet aromatic); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 189.4, 143.8, 130.1, 126.3, 121.9, 118.2, 143.1, 129.4, 118.2$; HRMS: (*m/z*) for $[C_{13}H_9NS_2 + H^+] = 244.0176$ (obs.), 244.0167 (calc.).

15. 3-(Naphthalen-2-ylmethyl)-3*H*-benzothiazole-2-thione [18] **(3o)**
Yellowish compound (1.30 g, 85%) melts at 163–164°C; $C_{17}H_{11}NS_2$; ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 6.29–6.98$ (4H, multiplet, aromatic), 7.08–7.75 (7H multiplet, aromatic), 4.68 (2H singlet); ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta = 193.5, 140.1, 139.5, 125.6, 124.8, 135.2, 133.5, 131.6, 127.3, 125.7, 124.8, 123.4, 118.7, 109.4\ 59.4$; HRMS (*m/z*) for $[C_{18}H_{13}NS_2 + H^+] = 308.0559$ (obs.), 308.0562 (calc.).

Disclosure statement

No potential conflict of interest was reported by the author(s).

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